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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,358	OON ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,10 and 13-42* is/are pending in the application.

4a) Of the above claim(s) *14,16-21,24,26-31,35 and 37-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,10,13,15,22,23,25,32-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11/8/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: 1449: 3/25/03; 4/14/03; 6/10/03.

DETAILED ACTION

1. This action is in response to the papers filed June 10, 2003; April 14, 2003; March 25, 2003; November 8, 2002. Currently, claims 1, 4-7, 10, 13-42 are pending.

2. The amendments to the Claims filed March 25, 2003 state that Claims 8-9, 11-12 are withdrawn. It is noted however that on July 30, 2002, Claims 8-9, 11-12 were cancelled. Therefore, the complete copy of the claims filed on March 25, 2003, appears to be inconsistent with the record. However, in an effort to expedite compact prosecution, Claims 1, 4-7, 10, 13-42 are pending.

3. This action is FINAL.

4. This action contains new grounds of rejection necessitated by amendment.

5. Any objection or rejection not reiterated herein, has been withdrawn in view of the amendments to the claims and applicants remarks.

Election/Restrictions

Restriction Requirement Applicable to All Groups:

6. The amendment filed March 25, 2003 amended the claims to recite limitations not previously claimed. The claims were amended to include detection of 8 various combinations of amino acid mutations. The methods require detection of patentably distinct mutations. Each sequence is patentably distinct because they are unrelated sequences, i.e. these sequences are unrelated because the protein encoded by these sequences differ in structure and in function and in biological activity. A restriction is

applied to each Group. For an elected Group drawn to amino acid sequences, the Applicants must further elect a single amino acid sequence.

The claims contains 8 individual, independent and distinct sequences in alternative form. Accordingly, these claims are subject to restriction under 35 U.S.C. 121 as outlined in 1192 O.G. 68 (November 19, 1996).

Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide sequences are presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq.

Applicant is required to select one of the individual sequences for examination. The search of the selected sequence may include the complements of the selected sequences and, where appropriate, may include subsequences within the selected sequences (e.g., oligomeric probes and/or primers).

Should applicant traverse on the ground that the nucleic acids are not patentably distinct, applicant should submit evident or identify such evidence now of record showing the species to be obvious variant or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over

the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other inventions.

It is noted that this is a **restriction** requirement and not an election of species.

During a telephone conversation with Shirley Chen on June 18, 2003 a provisional election was made with traverse to prosecute the invention of a mutation at amino acid position 131, claims 1, 4-7, 10, 13, 15, 22, 23, 25, 32-34, 36. Affirmation of this election must be made by applicant in replying to this Office action. Claims 14, 16-21, 24, 26-31, 35, 37-42 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

7. This application claims priority to foreign application Singapore 20004041-0, filed July 18, 2000. A certified copy of the application has been provided.

Claim Objections

8. Claims 1, 4-7, 10, 13, 15 are objected to because of the following informalities:

A) Claims 1, 4-7, 10, 13, 15 recite "a method for detecting mutation in". The claim appears to be missing an "a" prior to mutation. The claim may be amended to recite "a method for detecting a mutation in." Appropriate correction is required.

B) Claim 32 is directed to a method for evaluating whether a sample contains HBV that may be resistant be anti-HBV. The claim appears to contain a misplaced

word. It is presumed that the "be" prior to anti-HBV may have been intended to read "to." Appropriate correction is required.

New Matter

9. Claims 1, 4-7, 10, 13, 15, 22, 23, 25, 32-34, 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

With respect to Claims 1, 4-6, 10, 13, 15, 22-23, 25, 32-34, 36, in the amended claims, reference to "a first primer hybridizes under high stringency conditions to a region encoding the N-terminus of the major hydrophilic loop of HBV surface antigen and the second primers hybridizes under high stringency conditions to another region downstream from the C-terminus of the major hydrophilic loop of HBV surface antigen" are included. The amendment does not identify support in the specification for the amendment. Upon review of the specification, the specification does not describe or discuss "a first primer hybridizes under high stringency conditions to a region encoding the N-terminus of the major hydrophilic loop of HBV surface antigen and the second primers hybridizes under high stringency conditions to another region downstream from the C-terminus of the major hydrophilic loop of HBV surface antigen". Instead the specification describes primers hybridizing to a strand complementary to a target strand; primers which hybridize to regions corresponding to or flanking conserved nucleotide

sequence with or part of the nucleotide sequence encoding the HbsAg (page 3, lines 15-25). Figure 1 shows the structural organization of HBV surface antigen including the major hydrophilic loop. The major hydrophilic loop within the major HbsAG is from amino acid 100 to 160, and the conserved "a" determinant is from 124 to 1478 within SHBsAg (page 5, lines 28-37). However, this recitation in the specification does not teach "a first primer hybridizes under high stringency conditions to a region encoding the N-terminus of the major hydrophilic loop of HBV surface antigen and the second primers hybridizes under high stringency conditions to another region downstream from the C-terminus of the major hydrophilic loop of HBV surface antigen" as it pertains to the claimed invention. The concept of "a first primer hybridizes under high stringency conditions to a region encoding the N-terminus of the major hydrophilic loop of HBV surface antigen and the second primers hybridizes under high stringency conditions to another region downstream from the C-terminus of the major hydrophilic loop of HBV surface antigen" does not appear to be part of the originally filed invention. Therefore, "a first primer hybridizes under high stringency conditions to a region encoding the N-terminus of the major hydrophilic loop of HBV surface antigen and the second primers hybridizes under high stringency conditions to another region downstream from the C-terminus of the major hydrophilic loop of HBV surface antigen" constitutes new matter.

With respect to Claim 7, in the amended claims, reference to "a library of first primers", "a library of second primers" are included. The amendment does not identify support in the specification for the amendment. Upon review of the specification, the specification does not describe or discuss "a library of first primers", "a library of second

primers." Instead the specification describes using two primers. This description does not support a "library of first primers", "a library of second primers". The concept of "a library of first primers", "a library of second primers" does not appear to be part of the originally filed invention. Therefore, "a library of first primers", "a library of second primers" constitutes new matter.

With respect to Claim 13, a newly added Claim, reference to Orcein Red is included. The amendment does not identify support in the specification for the newly added limitation. The specification fails to teach Orcein Red as a reporter molecule. The specification does recite Texas Red. The concept of Orcein Red does not appear to be part of the originally filed invention. Therefore, "Orcein Red" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method for evaluating whether a sample contains HBV that may be resistant to anti-HBV drug treatment by detecting a mutation at position 131 where the identification of said mutation is indicative of the sample containing HBV that may be resistant to anti-HBV drug treatment.

The specification teaches the detecting and identification of HBV surface antigen mutants in Singapore adults and vaccinated infants with high anti-HBs levels but negative for surface antigen (Example 1, page 31). The results of the mutation analysis state that "there are also three cases here with the G130 D mutation (Table 2) that is recently found in one case report to be associated with lamivudine therapy (page 31, col. 30-32).

The art teaches the presence of T131N mutations in isolates of HBV.

Neither the art nor the specification teaches how to use the invention as broadly as claimed. The art does not teach any association of T131N with any resistance to anti-HBV drug treatment. Moreover, there is no indication in the specification that T131N mutation is associated with anti-HBV drug treatment resistance. The teachings of the specification do not establish that one could actually detect the presence of a mutation at position 131 as indicative that the sample contains HBV that may be resistant to anti-HBV drug treatment. While one could conduct additional experimentation to determine whether the presence of a mutation at amino acid position 131 is indicative of the sample containing HBV that may be resistant to anti-HBV drug treatment, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. The instant specification does

not provide any guidance to the presence of a mutation at position 131 and the anti-HBV drug lamivudine. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of a claimed invention. However, the closest prior art references do not provide any guidance to the detection of the presence of a mutation at position 131 as indicative that the sample contains HBV that may be resistant to anti-HBV drug treatment. It is unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly it would require undue experimentation for a skilled artisan to use the claimed invention.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 4-6, 10, 13, 15, 22-23, 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A1) Claims 1, 4-6, 10, 13, 15 are indefinite over the recitation "and the second primer hybridizes under high stringency conditions to another region downstream from the C-terminus of the major hydrophilic loop of HBV surface antigen" because the claim lacks proper antecedent basis. The claim requires "another region downstream from the C-terminus" however the claim does not require a first region downstream. Therefore, it is unclear what the recitation "another" is referring to.

B1) Claims 1, 4-7, 10, 13, 15, 22-23, 25, 32-34, 36 are indefinite over the recitation "a mutation at amino acid position 131." It is unclear what is being referred to as amino acid position 131. The specification fails to provide any particular amino acid sequence in the specification, drawings or the sequence listing. Therefore, it is unclear how position 131 relates to a sequence. Moreover, numbering systems vary in the art. It is not clear that position 131 of a particular amino acid in one numbering system is analogous to the same position in a different numbering system. Since the specification fails to provide any reference or flanking sequence which allow the artisan to determine what is meant by position 131, the metes and bounds of the claimed invention are unclear.

C1) Claims 22-23, 25 are indefinite over the recitation "the mixture" in step ii because "the mixture" lacks proper antecedent basis. The claim does not provide for a mixture. Therefore, it is unclear what "the mixture" is referring to. Additionally, step iii appears to contain steps. The step of determining is provided, but a step of identifying also appears to be provided. The "identification of said mutation" is not an active process step. Amending the claims to require an active process step of "identifying said mutation indicating that she sample contains HBV..." would provide more clarity and would particularly and distinctly claim the subject matter.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 15, 22, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni Minerva Medica, 1997).

This rejection is made based upon the numbering system of provided in the art. It is noted that the instant application does not provide a reference point for amino acid position 131, as required by the claims.

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer sequences, which represent highly conserved regions of the s-gene (Table 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Sequence analysis of isolates from 14 patients with isolated anti-HBc reactivity are illustrated (page 140). The Table lists the detection of N131T (a mutation at amino acid position 131). Therefore, Weinberger has determined whether the amplified products contain a mutation at amino acid position 131. Therefore, since Weinberger teaches every limitation of the claims, Weinberger anticipates the claimed invention.

Response to Arguments

The response traverses the rejection. The response asserts that Weinberger does not teach a method for detecting mutations at these specific amino acid positions (page 11 of response filed May 25, 2003). This argument has been reviewed but is not convincing because the reference teaches the presence of N131T mutation in several isolates of HBV in patients with isolated anti-HBc reactivity. Therefore, the indication of the presence of the mutations inherently is a method for detecting the mutations. Thus for the reasons above and those already of record, the rejection is maintained.

13. Claims 1, 15, 22, 25 are rejected under 35 U.S.C. 102(b) as being anticipated by McMahon et al. (Hepatology, Vol. 15, pages 757-766, 1992).

This rejection is made based upon the numbering system of provided in the art. It is noted that the instant application does not provide a reference point for amino acid position 131, as required by the claims.

McMahon et al. (herein referred to as McMahon) teaches a method for detecting genetic alterations in the gene encoding the major HbsAg. McMahon teaches that patients infected with either adw or ayw hepatitis B virus subtypes, amino acid differences for each variant allele were compared. McMahon teaches isolating DNA from serum samples and subjecting the samples to PCR. The reaction mixture was subjected to gel analysis (page 758, col 2). The DNA primers were chosen to delineate a 230-bp region comprising the a-determinant within the major S protein gene (page 760, col.2). McMahon teaches the presence of variant 131 (page 762, col. 1). As seen in Table 3, patient 010 contained a serum variant 131/145. Therefore, McMahon

inherently teaches a method of detecting a mutation at amino acid position 131 using primers and amplification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 10, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni Minerva Medica, 1997) in view of Mbayed et al. (J. Clinical Microbiology, Vol. 36, No. 11, pages 3362-3365, November 1998).

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer sequences, which represent highly conserved regions of the s-gene (Table 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Sequence analysis of isolates from 14 patients with isolated anti-HBc reactivity are illustrated (page 140). The Table lists the detection of N131T (a mutation at amino acid position 131). Weinberger teaches using primers which span the region comprising the nucleic acid encoding amino acid position 131. Therefore, Weinberger has determined whether the amplified products contain a mutation at amino acid position 131.

Weinberger does not specifically teach using primers of SEQ ID NO: 1 and 2.

However, Mbayed et al. teaches a method for detecting HBV nucleic acid target sequence in a sample, namely serum samples by amplifying the DNA using a nested PCR method to amplify part of the surface gene (page 3362, col. 2)(limitations of Claim 1). The extracted DNA was amplified with primers and then a second round of primer including primers HBS1 and HBS2. The HBS1 primer is 20 nucleotides in length. SEQ ID NO: 1 of the instant application comprises each of the 20 nucleotides of HBS1 with an additional T nucleotide on the 3' end. HBS2 is immediately downstream of SEQ ID NO: 2 of the instant application. As seen in Figure 1, SEQ ID NO: 2 is positions 668-690 of the Figure. These nucleotide positions are conserved among the Gualeguay HBV isolates. The amplification product was sequenced as a means of detection.

Mbayed teaches phylogenetic analysis shows "a clear different between the genotype distribution in Buenos Aires, a low-prevalence area, and that found in Gualeguay, Entre Rios, a high prevalence area" (abstract).

Therefore since the claimed oligonucleotides simply represent functional equivalents of the primers taught in the art, the skilled artisan would have been motivated to have designed additional primers which amplified HBV nucleic acids. Given the teachings of Weinberger as to the location of mutations of interest in the HBV genome and Mbayed aligning HBV isolates, the ordinary artisan would have recognized alternative primers which are also within conserved regions of the HBV nucleic acids would be equivalents to the HBS1 and HBS2 primers. The skill in the art at the time the invention was made was very high with respect to designing species or isolate specific primers and for using PCR to amplify regions known to contain mutations. Therefore, the ordinary artisan would have recognized that designing primers which flank a mutation, to further sequence and detect the mutation would have been obvious and routine to the ordinary artisan. Given the specific primers taught by Weinberger for detecting the T131N mutation, the skilled artisan would have been realized that alternative primers would represent functional equivalents. The ordinary artisan would therefore have the alignment of Mbayed to facilitate designing of nucleic acid primers which would function to amplify nucleic acids flanking the T131N mutation.

16. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni

Minerva Medica, 1997) and further in view of Mason et al. (Hepatology, Vol. 27 (6) 1736-42, June 1998).

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer sequences, which represent highly conserved regions of the s-gene (Table 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Sequence analysis of isolates from 14 patients with isolated anti-HBc reactivity are illustrated (page 140). The Table lists the detection of N131T (a mutation at amino acid position 131). Therefore, Weinberger has determined whether the amplified products contain a mutation at amino acid position 131.

Weinberger does not specifically teach reverse transcribing mRNA into cDNA prior to analysis.

However, Mason et al. (herein referred to as Mason) teaches hepatic nucleic acid extracts were assessed by PCR for either reverse-transcribed HBV RNA.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the methods of Weinberger with the teachings of Mason for reverse transcribing the HBV RNA prior to analysis to obtain DNA. The ordinary artisan would have been motivated to have reverse transcribed the HBV RNA into cDNA for the expected benefit of obtaining DNA which is more stable than RNA. Mason teaches that the reverse transcribed cDNA may be further analyzed by PCR.

17. Claims 5, 6, 7, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinberger et al. (Viral Hepatitis and Liver Disease, pages 138-143, Torino, Edizioni Minerva Medica, 1997) and further in view of Dattagupta (EP 0 374 665, June 27, 1990).

Weinberger et al. (herein referred to as Weinberger) teaches a method of amplification and detection of HBV DNA. Viral DNA was isolated from serum. Primer sequences, which represent highly conserved regions of the s-gene (Table 1) were added to the template DNA. Both the first and second round amplification comprised an initial denaturation step. The amplification was detected and visualized on agarose gels (page 139, col. 1). Sequence analysis of isolates from 14 patients with isolated anti-HBc reactivity are illustrated (page 140). The Table lists the detection of N131T (a mutation at amino acid position 131). Therefore, Weinberger has determined whether the amplified products contain a mutation at amino acid position 131.

Weinberger does not specifically teach the use of a labeled primer or a primer attached to a solid support in combination with a primer in solution.

However, Dattagupta specifically teaches a method for amplifying and detecting specific target nucleic acid sequences in a sample by contacting a first primer and a second primer with nucleic acid where one primer is immobilized and the other primer is labeled (Table 1, embodiments (3) and (6); page 4)(limitations of Claims 6-7). Dattagupta teaches that embodiments (3) and (6) of Table 1 may be assayed for using detection of the label on the support to determine the presence of the test amplified nucleic acid; by hybridization with a specific probe; extent of incorporation of a labeled

nucleic acid residue; or a post extension agglutination reaction (page 4, lines 36-43). Dattagupta teaches that in an "immobilizable/labeled system, the biotin would be present on one primer and a label such as fluorescein would be on the second primer, following amplification by thermocycling, the biotin containing product could be immobilized" (page 7, lines 12-16)(limitations of Claim 5). Dattagupta provides that the improvement of the method over the Mullis patent is at least one of the primers is immobilized (page 3, line 34-35). Additionally, Dattagupta teaches that the PCR method is significantly improved by the use of immobilized or immobilizable nucleic acid primers. The final amplified products are already immobilized or specifically immobilizable without significant loss in efficiency of amplification (page 5, lines 9-12).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the PCR methods of Weinberger with the teachings of Dattagupta of the improvements of immobilization for detection of PCR products. The ordinary artisan would have been motivated to have immobilized and labeled the primers of Weinberger for the express benefits taught by Dattagupta. Dattagupta teaches that the "PCR method is significantly improved by the use of immobilized or immobilizable nucleic acid primers. The final amplified products are already immobilized or specifically immobilizable without significant loss in efficiency of amplification." Therefore, the ordinary artisan would have been motivated to have immobilized and labeled the primers in the HBV detection methods for the express benefit of improved detection.

Conclusion

18. No claims allowable over the art.

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg
Jeanine Goldberg
June 19, 2003

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600